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Appl. No. : National Phase Entry of PCT/EP2004/002810  
Applicant : Dieter HERRMANN et al  
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Examiner :

Docket No. : 2970-125  
Customer No. : 6449  
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**PRELIMINARY AMENDMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Please enter the following amendments before calculation of the filing fee and examination of the merits.

**Amendments to the Specification** begin on page 2 of this paper.

**Amendments to the Claims** begin on page 3 of this paper.

**Remarks** begin on page 10 of this paper.

**Amendments to the Specification:**

Page 1, before line 1, insert:

**Cross Reference to Related Application**

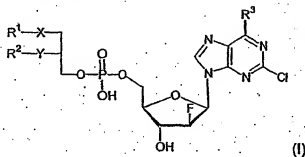
This application is a 35 USC § 371 National Phase Entry Application from PCT/EP2004/002810, filed March 18, 2004, and designating the United States, which claims the benefit of provisional application no. 60/456,003 filed March 19, 2003.

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Original) A nucleotide derivative of formula 1



wherein

R<sup>1</sup> is selected from the group consisting of a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylmercapto, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl or C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl groups;

R<sup>2</sup> is selected from the group consisting of hydrogen, a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, which is unsubstituted or substituted at least once by halogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylmercapto, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl or C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl groups;

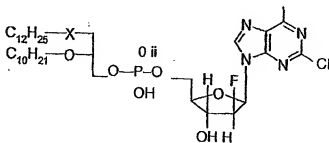
R<sup>3</sup> is amino or OR<sup>4</sup>, wherein R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl;

X is selected from the group consisting of a sulfur atom, a sulfinyl group and a sulfonyl group;

Y is oxygen;

whereby when R<sup>3</sup> is amino, said amino group may be unsubstituted or substituted by a known amino protecting group, their tautomers, their optically active forms and racemic mixtures, and their physiologically acceptable salts of inorganic and organic acids or bases.

2. (Original) The nucleotide derivative according to claim 1, wherein R<sup>1</sup> is a straight-chain C<sub>8</sub>-C<sub>15</sub> alkyl group, which is unsubstituted or substituted by a C<sub>1</sub>-C<sub>6</sub> alkoxy or a C<sub>1</sub>-C<sub>6</sub> alkylmercapto group.
3. (Original) The nucleotide derivative according to claim 1, wherein R<sup>2</sup> represents a straight-chain C<sub>8</sub>-C<sub>15</sub> alkyl group, which is unsubstituted or substituted by a C<sub>1</sub>-C<sub>6</sub> alkoxy or a C<sub>1</sub>-C<sub>6</sub> alkylmercapto group.
4. (Currently Amended) The nucleotide derivative according to ~~claims 1 to 3~~ claim 1, wherein R<sup>3</sup> is OCH<sub>3</sub>.
5. (Currently Amended) The nucleotide derivative according to ~~the claims 1-4~~ claim 1, wherein the compound is:

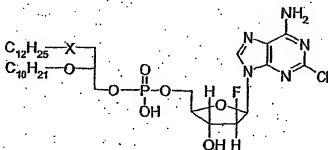


wherein X is sulfur, sulfinyl or sulfonyl.

6. (Currently Amended) The nucleotide derivative according to claims 1 to 3 1,

wherein  $R^3$  is  $NH_2$ .

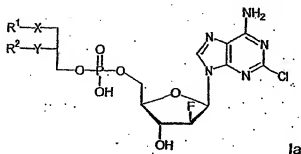
7. (Currently Amended) The nucleotide derivative according to claims 1 to 3 or 6 1, wherein the compound is:



wherein X is sulfur, sulfinyl or sulfonyl.

8. (Currently Amended) A pharmaceutical composition comprising at least one compound according to claims 1 to 7 1 in combination with a pharmaceutically acceptable adjuvant or vehicle.
9. (Currently Amended) A method for treating malignant tumors comprising administering to a patient in need of such treatment an amount of a compound according to claims 1 to 7 1 effective to treat said tumors.
10. (Original) The method according to claim 9, wherein said tumor is selected from the group consisting of carcinomas, sarcomas or leukemias.
11. (Original) A method for treating malignant tumors comprising administering to a patient in need of such treatment an amount of the composition according to claim 8 effective to treat said tumors in fixed or free combination with other anticancer agents.

12. (Original) A method of synthesis of compounds of the formula Ia:



wherein  $R^1$  is a straight-chain or branched, saturated or unsaturated alkyl residue having 1-20 carbon atoms, optionally mono- or polysubstituted by halogen,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylmercapto,  $C_1$ - $C_6$  alkoxycarbonyl,  $C_1$ - $C_6$  alkylsulfinyl or  $C_1$ - $C_6$  alkylsulfonyl groups;

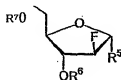
$R^2$  is hydrogen, a straight-chain or branched, saturated or unsaturated alkyl chain having 1-20 carbon atoms, optionally mono- or polysubstituted by halogen,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylmercapto,  $C_1$ - $C_6$  alkoxycarbonyl or  $C_1$ - $C_6$  alkylsulfonyl groups;

X is selected from the group consisting of a sulfur atom, a sulfinyl group and a sulfonyl group;

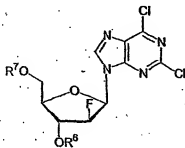
Y is oxygen;

comprising:

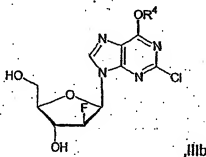
(a) reacting 2,6-dichloroadenine with an arabinofuranosyl derivative of the formula:



wherein  $R^5$  is bromo or chloro and  $R^6$  and  $R^7$  are protecting groups, in the presence of a hindered potassium base and a solvent to form the dichloro-purine nucleoside derivative:

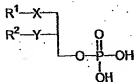


(b) subjecting said dichloro purine nucleoside derivative to conditions to provide for deprotection and an aromatic nucleophilic substitution reaction to provide the 6-alkoxy-2-chloro purine nucleoside derivative of general formula IIIb:

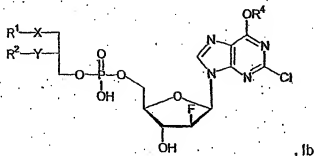


wherein  $R^4$  is  $C_1$ - $C_8$  alkyl;

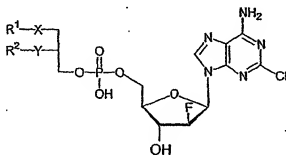
(c) reacting said 6-alkoxy-2-chloro purine nucleoside derivative with an activated form of the compound:



in an inert solvent to provide the conjugated 6-alkoxy-2-chloro purine nucleotide derivative of general formula 1b:



(d) subjecting said conjugated 6-alkoxy-2-chloro purine nucleotide derivative to conditions that provide for aminolysis to prepare the conjugated 2-chloroadenine derivative:



13. (Original) The method of claim 12 wherein, said hindered potassium base is potassium t-butoxide or potassium f-amylate.
14. (Original) The method of claim 12, wherein said solvent for reacting said 2,6-dichloroadenine and said arabinofuranosyl derivative is a mixture of acetonitrile, f-butanol and 1,2-dichloroethane.
15. (Original) The method of claim 12, wherein R<sup>4</sup> is methyl.



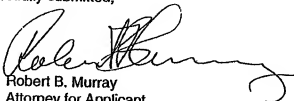
16. (Original) The method of claim 12, wherein  $R^5$  is bromo.
17. (Original) The method of claim 12, wherein  $R^6$  and  $R^7$  are independently acetyl or benzoyl.
18. (Original) The method of claim 12, wherein  $R^1$  and  $R^2$  are individually a straight-chain  $C_8$ - $C_{15}$  alkyl group, which is unsubstituted or substituted by a  $C_1$ - $C_8$  alkoxy or a  $C_1$ - $C_8$  alkylmercapto group.
19. (Original) The method of claim 12, wherein  $R^1$  is  $C_{12}H_{25}$  and  $R^2$  is  $C_{10}H_{21}$ .

**REMARKS**

The above amendments to the specification and claims have been made to put the application in better condition for examination. No new matter has been added.

Respectfully submitted,

By



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